

Howard M. GREY *et al.*
Scr. No. 08/349,177
Page 4

53. The composition of claim 48, wherein the amino acid at position 7 from the N-terminus is not an amino acid selected from the group consisting of R, K and H.

54. The composition of claim 48, wherein the amino acid at position 8 from the N-terminus is not an amino acid selected from the group consisting of D, E, R, K and H.

55. The composition of claim 48, wherein the amino acid at position 9 from the N-terminus is not an amino acid selected from the group consisting of R, K and H.

REMARKS

The Invention

The present invention is based on the discovery of novel binding motifs that allow peptides to bind to HLA-A2.1 MHC products. Using these new motifs, one of skill can now screen sequences of particular protein antigens for the presence of motifs that allow peptides to bind particular A2.1 gene products. The corresponding peptides are then made and tested for their ability to bind the MHC molecules. As explained in detail below, essentially all those peptides that bind with affinity above a certain threshold are capable of inducing a CTL response against the antigen. By providing a means for identifying motif-bearing subsequences that are immunogenic, the invention greatly reduces the number of peptides to be screened for final use in treatment of disease and other uses. The compositions of the invention are useful in diagnosing, preventing, or treating a number of pathological states such as viral diseases and cancers.

The Amendments

New claims 38-55 correspond to originally filed claims 1-18. These claims are submitted in response to the Examiner's requirement that Applicants resubmit claims drawn to the invention that was addressed in the previous Office Action. New claim 37 is a linking claim which encompasses both the 9-mer peptides of claims 38 and 39 (original claims 1 and 2) and the 10-mer peptides of claim 48 (original claim 11).

Support for the claim element of claims 37-39 and 48 which specifies that it is the binding motif, rather than the peptide itself, which has nine or ten residues, is found at, for

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 5

example, page 4 lines 34-36 ("The term 'motif' refers to the pattern of residues in a peptide of defined length, usually about 8 to about 11 amino acids, which is recognized by a particular MHC allele."). The remaining differences between claims 38-55 and the corresponding originally filed claims are clerical in nature (claim dependencies are changed to reflect the new claim numbering, and typographical errors in original claims 2 (semicolon replaced with period at end of new claim 39) and 15 ("positon" is replaced with --position-- in corresponding new claim 52) are corrected. Thus, entry of claims 38-55 does not add new matter to the application.

Support for the terms defining the binding affinity of the claimed peptides is found in parent application 08/159,184, which is incorporated by reference in the first paragraph on page 1 of the present application (relevant pages from the '184 application were enclosed with Applicants' response filed June 23, 1997). On page 38, line 25, to page 39, line 24, of the '184 application, the methods by which binding affinities are determined are described. As explained there, the affinities are determined relative to a reference peptide, FLPSDYFPSV (*see*, page 39, lines 10-13). In Table 5 on page 43 and the text in the first paragraph of page 44, the categories of high, intermediate and weak binders are defined by the ratio of the apparent IC50 of the reference peptide compared to the test peptides. There, it is explained that the ratio of reference peptide IC50 to test peptide IC50 must be at least 0.01, for a peptide to be considered an intermediate or high binder. This is, of course, equivalent to describing the dissociation constant (which as explained on page 38, line 26-28, approximates IC50) of the test peptide as less than 100 times that of the reference peptide, as recited in the claims. Support for the term "isolated" in claim 37 is found at, for example, page 5 lines 8-18. Thus, entry of claim also does not add new matter to the application.

The Restriction Requirement

Claims 38-47 correspond to originally filed claims 1-10 (compositions comprising nine-mer peptides), which claims Applicants elected, with traverse, pursuant to a species election requirement. New claims 48-55 correspond to originally filed claims 11-18, which were not elected. The Examiner has stated that claims to the nonelected species (compositions comprising ten-mer peptides) will receive consideration upon allowance of a generic claim (Office Action

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 6

mailed 12/23/96, page 2). Accordingly, Applicants have requested entry of new claim 37, which is a linking claim which is generic to the two species.

In the Communication mailed 10/1/97, claims 19-36 are asserted to be drawn to an invention that is patentably distinct from the invention that was previously under consideration in the previous Office Action. Applicants respectfully submit that examination of the method claims 19-36 in addition to the previously elected composition claims would create little or no additional burden on the Examiner. A search for references which describe peptides encompassed by the compositions of claims 37-55 would necessarily identify all references that describe the use of the peptides in the methods of claims 19-36. According to MPEP § 803, "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." Therefore, Applicants respectfully request that the Examiner examine all claims pending in this application.

The 35 USC § 101 Rejection

Originally filed claims 1-10 were rejected under 35 USC § 101 for allegedly reading on naturally occurring peptides found on the surface of HLA-A2.1 positive cells. Newly added claim 37, upon which claims 38-55 depend, specifies that the immunogenic peptide is "isolated," which is defined in Applicants' specification as "material which is substantially or essentially components which normally accompany it as found in its native state." Thus, this claim element excludes naturally occurring peptides found on HLA-A2.1 positive cells and obviates the rejection.

The 35 USC § 112, First Paragraph Rejection

Originally filed claims 1-10 were rejected under 35 USC § 112, first paragraph as allegedly encompassing subject matter which was not described in the specification sufficiently to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Applicants' traversal of this rejection with regard to claims 19-36 in their response mailed 6/23/97 (pages 6-11) is equally applicable to claims 38-

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 7

47 (which correspond to originally filed claims 1-10), and also to claims 37 and 48-55. For the Examiner's convenience, the relevant portions of the previous response are reproduced below.

In the rejection, the Examiner alleges that claims directed to "immunogenic" peptides are not enabled by the specification. In particular, the Examiner relies on two references which allegedly teach that binding to MHC is not definitive evidence that a peptide is immunogenic. In addition, the Examiner notes that the specification refers to "allele-specific" motifs, but cites references that show some peptides within the scope of the claims bind to more than one allele. These two points are addressed below.

Immunogenicity of the peptides of the invention.

The Examiner cites two papers (Celis *et al.*, *Mol. Immunol.* 31:1423 (1994) and Ramensee *et al.*, *Immunogenetics* 41:178 (1995)) for allegedly teaching that peptides that bind a particular MHC gene product are not necessarily immunogenic. The rejection is not apparently based on an assertion that any particular procedure required to practice the claimed methods using the claimed compositions is unpredictable or even difficult to carry out. For example, applicants do not understand the rejection to be based on an allegation that preparation of peptides, or the preparation and administration of pharmaceutical compositions containing the peptides or nucleic acids that encode them is unpredictable. Rather, the rejection is based on a concern that, if one of skill carries out these steps a useful result (*e.g.*, induction of an immune response) will not be obtained.

As explained in MPEP §2107(d), a close relationship exists between 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. In particular, the MPEP states:

[T]he Federal Circuit recently noted, "[o]bviously, if a claimed invention does not have utility, the specification cannot enable one to use it." *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. ***It is equally clear that a rejection based on "lack of utility," whether grounded upon 35 U.S.C. 101 or 35 U.S.C. 112, first paragraph, rests on the same basis (i.e., the asserted utility is not credible).*** MPEP § 2107(d) (emphasis added).

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 8

Applicants understand the rejection to be an argument that administration of the claimed compositions would not necessarily induce an immune response against the desired antigen, and thus lack a credible utility under the patent laws. As a result, according to the Examiner, such claims are not enabled under §112, first paragraph, because undue experimentation would allegedly be required to achieve a useful result. As explained below, the underlying conclusion that a credible utility, as defined by the patent laws, has not been shown, cannot supported after consideration of the present disclosure and the state of the art at the time of the invention.

As noted above, the pending claims are directed to peptides that have high or intermediate affinity (defined in the first paragraph of page 44, of the '184 application) for HLA-A2.1 products, and methods of using such peptides. As explained in the specification, a correlation exists between degree of MHC binding and immunogenicity (*see*, page 2, lines 23-27). The specification cites references, available at the time the application was filed, demonstrating that such a correlation exists. For example, Sette *et al.*, *Proc. Nat. Acad. Sci. USA* 86:3296 (1989) showed that MHC allele specific motifs could be used to predict MHC binding capacity. Schaeffer *et al.* *Proc. Nat. Acad. Sci. USA* 86:4649 (1989) showed that MHC binding was related to immunogenicity. Several authors (De Bruijn *et al.*, *Eur. J. Immunol.*, 21:2963-2970 (1991); Pamer *et al.*, *Nature*, 353:852-955 (1991)) provided preliminary evidence that class I binding motifs can be applied to the identification of potential immunogenic peptides in animal models.

The Examiner, in contrast, relies on two references which allegedly show that no such correlation exists. As an initial matter, applicants note that both papers were published *after* the effective filing date of the present application. Thus, their ability to establish the state of the art *at the time of the invention* is questionable, at best. Applicants respectfully submit that in the absence of showing that references available at the time of the invention provide the teaching alleged to found in these references, the rejection is improper and should be withdrawn.

Nonetheless, a careful reading of these references shows that they support, rather than refute, the conclusion that compositions and methods of the invention have a credible utility, as defined under the patent laws. For instance, the authors of the Celis *et al.* paper

Howard M. GREY *et al.*
Scr. No. 08/349,177
Page 9

(including two inventors of this invention) screened the tumor associated antigen MAGE-1 using A2.1 motifs that included the motifs claimed here (*see*, Table 1). As explained on page 1427, column 1, peptides found in the initial screen were prepared and analyzed in quantitative binding assays essential identical to those used in the present invention. As explained in the second column of page 1427, peptides were divided into the same categories of high, intermediate and weak binders as used in the present invention¹. As can be seen in Table 3, A2.1 motif identified a total of 11 high or intermediate binders out of a total of 65 peptide identified in the protein. Since the MAGE-1 protein contains a total of 309 residues (*see*, page 1426, first column), in the absence of motifs, hundreds of peptides (all possible 9-mers and 10-mers) would have to be prepared and screened. Instead, using the motifs described in the paper, only 65 peptide were tested and the final number of candidates was then reduced to 11, based on binding.

As is evident from this paper, the authors were not identifying peptides with high affinity as an academic exercise, but because they recognized that such peptides are useful to induce immune responses against MAGE-1. As noted in the sentence bridging columns 2 and 3 of page 1427, over 90% of T cell epitopes or naturally processed peptides bind HLA molecules with an affinity of 50 nM or less. Thus, the authors reasonably concluded that those peptides showing good binding characteristics are immunogenic and are extremely likely to be used as vaccines for treatment of cancer. The Examiner quotes a section of this paper out of context to assert that the work described in this paper is not considered by the authors to be useful in the identification of immunogenic peptides. The language merely sets forth the further testing that, of course, must be carried out to definitively determine which peptides will be used for the ultimate purpose of treatment or diagnosis of disease in humans.

The language quoted from page 182 of the Rammensee *et al.* paper is also quoted out of the context. The authors state that *historically* binding assays have lead to obsolete

¹ As explained on page 38, lines 10-13 of the '184 application, the average IC₅₀ (or dissociation constant) of the reference peptide is 5nM. Since the claimed peptides (high and intermediate binders as defined on page 43 of the '184 application) have a dissociation constant of less 100 times that of the reference peptide, they have a dissociation constant of 500 nM or less. This corresponds exactly to the cut-off used in the Celis *et al.* paper to identify high and intermediate binders.

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 10

results, but emphasize in the next sentence that such assays have improved. In the next section on page 182, the authors state that the main purpose for which information about binding affinities can be used is to identify T cell epitopes. The authors then describe the general approach used in the present invention to identify such peptides. Thus, applicants respectfully submit that the authors of both papers recognized the importance of motifs to define peptide antigens useful for treatment of human disease. Neither paper calls into question the value of the claimed compositions and methods for the ultimate purpose of treating or diagnosing disease in humans.

As the Examiner is undoubtedly aware, a definitive showing of human efficacy has *never* been required by the patent laws. To satisfy the requirements of the patent laws, an invention must have "real world" utility (*see*, MPEP §2107). As noted by the Courts:

"practical utility" is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public."

Nelson v. Bower and Crossley 206 USPQ 206 (CCPA 1980).

Applicants respectfully submit that the motifs and methods of invention greatly simplify the identification of peptide-based vaccines and other treatments and therefore provide immediate benefit to the public. As shown above in the *Celis et al.*, without the motifs identification of such peptides requires making and screening *every possible* peptide sequence from a given antigen. The present invention is based on the discovery of a simple process by which only the most immunogenic peptides of a given antigen are immediately identified. The claimed compositions and methods therefore have a credible, practical utility which greatly advances the art. Nothing has been provided to show that such a utility is not sufficient to meet the requirements of the patent laws.

Applicants further respectfully submit that the Examiner's conclusory statements concerning a possible but undemonstrated lack of utility for some of the claimed peptides are insufficient as a matter of law to overcome the presumption of utility. Applicants have identified motif-bearing subsequences present in known amino acid sequences of several biologically important proteins, and synthesized these peptides. (*See*, Tables 3 and 4 of the specification).

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 11

Furthermore, Applicants have demonstrated that peptides bearing the appropriate motif both bind to the predicted class I MHC allelic products and produce cytotoxicity in CTL assays *in vitro*. (see, Example 10 on pages 73-77 of the '184 application). Indeed, peptides having the motif were further tested in transgenic mice expressing human HLA-A2.1 molecules. As shown in Table 23 of the '184 application, binding and immunogenicity were closely correlated. As noted at the bottom of page 76, peptides having a binding ratio of at least 0.01 are capable of inducing CTL immune responses.

The present rejection is apparently based on a concern that a large number of possible different peptides that could fit the binding motif and that some of these might be inoperative. As noted above, the claims are now directed to compositions which comprise high or intermediate binding peptides. It is well settled that:

For a proposed claim to be unpatentable, the law requires that the number of inoperable embodiments be significant in numbers and **not readily ascertained** by those of skill. *In re Cook and Merigold*, 169 U.S.P.Q. 298, 301-302 (C.C.P.A. 1971).

Applicants respectfully, submit that the instant rejection does not take into account that the specification teaches a person of ordinary skill how to readily determine which embodiments are inoperative. The specification in fact provides extensive teaching for one of skill "readily ascertain" which peptides are immunogenic. As noted above, the application teaches that there is a distinct correlation between peptide binding and immunogenicity. Applicants teach binding assays that directly measure the affinity of the peptides for a given MHC allele. Thus, one of skill using the present disclosure and methods known in the art at the time could readily ascertain peptides having the desired properties. The Examiner has not provided sufficient reason or evidence to show why the claimed methods and compositions lack utility.

Thus, for all the foregoing reasons, Applicants assert that a utility-based rejection of either the pending claims is improper, particularly in view of the amendments and additions to the claims, and they request that the § 112 rejection be withdrawn.

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 12

"Allele-specific motif"

Applicants respectfully traverse the rejection based on the assertion that the claims read on "allele-specific" motifs. Applicants note that neither the rejected claims nor the pending claims are explicitly directed to "allele-specific" motifs. Instead the claims are directed to peptides containing certain defined structural features that allow them to bind to A2.1 molecules, and methods of using such peptides. Nothing in the claims requires that the peptides bind these molecules exclusively. The fact that peptides that bind A2.1 molecules might also bind other alleles does not detract from their utility in the claimed methods and compositions. In the absence of an explanation as to why such cross reactivity is detrimental to the claimed methods, the rejection should be withdrawn.

The 35 USC § 112, Second Paragraph Rejection

Originally filed claims 1-10 were rejected under 35 USC § 112, second paragraph as being indefinite in their recitation of "at the C-terminal position." Applicants respectfully submit that the term would be understood by those of skill in the art to refer to the terminal residue of the binding motif. Nonetheless, to expedite prosecution, the pending claims are directed to peptides in which the recited residues occur at the "C-terminus" of the motif, thus rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

The 35 USC § 102(b) Rejection

Originally filed claims 2, 4, 6 and 10 were rejected under 35 USC § 102(b) as allegedly being anticipated by Sette *et al.*, *J. Immunol.* 147: 3893-3900 (1991). The previously rejected claims correspond to new claims 39, 41, 43, and 47. The new claims, however, explicitly exclude the peptide described by Sette *et al.* The courts have long held that amendments to claims to specifically exclude prior art species from a claimed genus is proper under the patent laws (*see, e.g., In re Johnson and Farnham* 194 USPQ 187 (CCPA 1977)). In light of the above, applicants believe the present rejection should be withdrawn.

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 13

The 35 USC § 103 Rejection

The rejection of the claims as being obvious over Falk *et al.* *Nature* 351:290 (1991) is respectfully traversed. The rejection is apparently based on the presumed contents of a composition containing a large mixture of unsequenced peptides eluted from A2.1 molecules. According to the Examiner, such a mixture *might* contain peptides useful in the claimed methods. The Examiner's position is apparently based on the assumption that a disclosure that peptides can be eluted from an MHC molecule is the same as disclosure of a motif that allows peptides to bind that molecule. Applicants respectfully disagree.

It is well settled that the teachings of a prior art reference must be considered in their entirety. Moreover, the prior art must be considered in a manner consistent with its interpretation by one of skill at the time of the invention.

The present claims are directed to compositions which include peptides having certain defined structural features that are nowhere disclosed or suggested in the cited reference. The Examiner provides no reasoning or evidence to show why one of skill would select these peptides from the large collection of eluted peptides to use in the claimed methods. Indeed, the Falk *et al.* paper actually *teaches away* from the claimed compositions because they teach that peptides with a completely different motif (set forth in Table 4) are good binders and hence immunogenic. Thus, one of skill reading this reference, at the time of the invention, would prepare peptides completely distinct from those used in the claimed compositions.

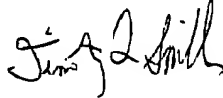
Applicants respectfully submit that the Falk *et al.* paper when properly read as it would have been understood by one of skill in the art at the time of the invention, would not lead such a person to the claimed invention. In the absence of a showing why one of skill would be motivated to screen for peptides with a motif nowhere disclosed in this paper the rejection is improper and should be withdrawn.

Howard M. GREY *et al.*
Ser. No. 08/349,177
Page 14

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Respectfully submitted,



Timothy L. Smith, Ph.D.
Reg. No. 35,367

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
(415) 576-0200
Fax (415) 576-0300